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Statistical analysis plan of PROWESS SHOCK study

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Dear Editor,

The steering committee (SC) of the PROWESS SHOCK study has put in place processes that should guarantee independence and transparency to resolve the controversies surrounding the investigation and use of drotrecogin alfa (activated), thus serving the best interests of our patients [1].

The SC anticipated that the mortality rates from sepsis may be decreasing in response to improved quality of care [2] with a consequent influence on the sample size calculation for the PROWESS SHOCK study. We have described the impact of a falling placebo mortality rate and how the sample size would need to be changed to maintain 80% power to detect a 20% relative mortality reduction with drotrecogin alfa (activated) [2]. Accordingly, we employed a conditional power design to resize the study if aggregate mortality observed for the first 750 patients was lower than the anticipated 31.5% [1, 3].

Recent reports do indeed suggest temporal improvements in sepsis mortality. A multicenter demonstration project of a sepsis treatment "bundle" demonstrated a 5.4% absolute decrease in hospital mortality in the 15,022 subjects treated between 2005 and 2008 [4]. The australian and new zealand intensive care (ANZIC) research network investigators demonstrated a reduction in hospital mortality from 35.6% to 21.2% ($n = 7{,}250$) over an 8-year period ending in 2005 [5]. Recent trials have also reported lower than expected mortality. An international trial of TAK-242, a TLR-4 antagonist, enrolled 274 patients from 94 medical centers with septic shock or sepsis requiring mechanical ventilation and noted a placebo 28-day mortality of 28% despite a sequential organ failure assessment (SOFA) score over 8. The predicted mortality for sample size estimation was 40% [6]. A phase 2 trial of eritoran tetrasodium (E5564) enrolled adults with severe sepsis. The average predicted mortality was 53%, yet the observed 28-day mortality was 24–25% [7].

On 12 May 2010 the SC reviewed the aggregate baseline characteristics and 28-day mortality for the first 753 subjects in the PROWESS SHOCK study. At baseline, the mean number of organ failures was 3.5, all subjects were vasopressor dependent throughout the 17-h (mean) pre-enrollment period, 72% had renal dysfunction, and the (mean) total SOFA score was 9. The selected population therefore has a higher disease severity compared with PROWESS [8]. However, the aggregate mortality was 27.6%. Accordingly, the SC approved a protocol-specified increase in sample size from 1,500 to 1,696 subjects (848 per group).

The analyses for the primary publication will be done by an independent academic statistical center [the Duke Clinical Research Institute (DCRI), Drs. Kerry Lee and Robert Califf]. Furthermore, the statistical analysis plan (SAP) has been developed in collaboration with the steering committee, the sponsor, and the DCRI, and the final plan submitted to the Food and Drug Administration (FDA) in February of this year, prior to the first interim analysis by the data monitoring committee (DMC). Furthermore, and in accordance with recent calls for publication of analysis plans in advance of study completion, we are attaching the entire SAP as a supplement to this letter [9].

As of the end of June we have enrolled 971 subjects into the trial, with the majority being enrolled in Europe. Based on the current rate of enrollment and the assumption that the DMC will allow the study to continue to completion, we anticipate that the study will be completed in spring or summer 2011.

We wish to thank all our study subjects and their families, as well as our dedicated co-investigators and research coordinators and the sponsor, Eli Lilly, for their participation, support, and hard work on this important study.

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